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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/789,303	02/26/2004	Kelly Reed Clark	28335/40012	8089

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EXAMINER	
BURKHART, MICHAEL D	
ART UNIT	**PAPER NUMBER**
1633	

DATE MAILED: 04/04/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/789,303	CLARK ET AL.	
	Examiner	Art Unit	
	Michael D. Burkhart	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *1/3/2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-14,18,19 and 21-38* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-14,18,19 and 21-38* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *1/3/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Receipt and entry of the amendment dated 1/3/2006 is acknowledged. Upon entry of the amendment, claims 1-14, 18, 19 and 21-38 are pending and under examination.

Information Disclosure Statement

The Xiao et al reference on the IDS of 1/3/2006 has been crossed through because it was considered and made of record in the Office Action of 7/9/2005.

Claim Objections

Claim 34 is objected to because of the following informalities: "of any of claim 21" should be "of claim 21." Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 2, 9, 10-14, and 21-38 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 recites a rAAV-producing cell the "overexpresses AAV Rep 52 and Rep 40 proteins" in the last two lines. It is unclear what the point of reference is for the overexpression of the Rep52/40 proteins: overexpressed compared to what? For example is the overexpression compared to Rep52/40 expression mediated by the wild type AAV promoter, or to expression mediated by a constitutive, heterologous promoter such as a CMV promoter? For this reason,

the metes and bounds of the subject mater are unclear. This rejection affects all dependent claims. **This is a new rejection.**

Claim 9 recites a rAd "derived from" simian Ad SV-20. It cannot be determined how close to the original or wild-type SV-20 the derivative rAd might be. Therefore, the metes and bounds of the claimed subject matter are unclear. This rejection is maintained for reasons of record (Office Action of 7/29/05) and for reasons set forth below.

Response to Arguments

Applicant's arguments filed 1/3/2006 have been fully considered but they are not persuasive. Applicants argue that: 1) the term "derived from" indicates the claimed adenovirus vectors were constructed using simian adenovirus SV-99; and, 2) methods to modify adenoviruses in order to construct adenoviral vectors are well known in the art.

Regarding 1), it is unclear how the use of SV-99 can be construed to the instant claims, which recite SV-20. Even if the claimed SV-20 were used, it remains unclear how close to the original SV-20 the claimed derivative(s) might be. For example, how much of the SV-20 genome could be deleted, or replaced with foreign sequences, and the rAd still be considered "derived" from SV-20? Regarding 2), methods to modify wild-type adenoviruses are indeed well-known in the art, but this issue was not in contention and this argument appears more suited as a response to a U.S.C. 112 1st¶ enablement rejection. One of skill in the art could indeed modify wild-type adenoviruses using established methods. However, what is unclear is the extent of such modification required to read on the claimed subject matter.

Claim 10 recites a method of generating a rAAV-producing cell by introducing "into a cell comprising a rAAV genome and AAV rep-cap proteins supplemental AAV Rep 52 and Rep 40 proteins" in step a). It is unclear what the cell comprises and what is being introduced. For example, does the cell comprise the rAAV genome, AAV rep-cap and supplemental AAV Rep 52/40 proteins, or only the rAAV genome and AAV rep-cap proteins? Therefore, the metes and bounds of the claimed subject matter are unclear. It would be remedial to recite step a) as "introducing supplemental Rep 52 and Rep 40 proteins into a cell comprising a rAAV genome and AAV rep-cap proteins." This rejection affects all dependent claims. **This is a new rejection.**

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 9, 14, and 19 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. This rejection is maintained for reasons made of record in the previous Office Action and for reasons set forth below.

The invention appears to employ novel biological materials, specifically the simian adenovirus strain deposited as ATCC No. VR-199. Since the biological materials are essential to the claimed invention they must be obtainable by a repeatable method set forth in the

specification or otherwise readily available to the public. If the biological materials are not so obtainable or available, a deposit of the biological materials may satisfy the requirements of 35 U.S.C. § 112. The specification does not disclose a repeatable process to obtain the biological material and it is not apparent if the biological materials are readily available to the public.

Response to Arguments

Applicant's arguments filed 1/3/2006 have been fully considered but they are not persuasive. Applicants argue that the claimed ATCC VR-199 is currently available to the public from the ATCC, that applicants did not deposit the strain, and thus the rejection should be withdrawn. This is not found convincing because the ATCC is under no obligation to make the claimed strain available to the public for the time period set forth in the previous Office Action (i.e. 30 years or 5 years after the last request or for the effective life of the patent, whichever is longer) and applicants have no alternative way of ensuring the availability of ATCC VR-199. It is considered that recitation of "ATCC VR-199" in the claims is superfluous and that claiming "simian Ad SV-20" is sufficient. Removal of the reference to an ATCC number would obviate the rejection.

Claims 3-14, 21-29, and 31-38 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of producing rAAV or rAAV-producing cells by transfection or transformation of cells with nucleic acids encoding the desired proteins, does not reasonably provide enablement for such methods by "providing" AAV helper functions (as recited in claim 3) or introducing proteins into a cell (claim 10). The specification does not

enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

The test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the application coupled with information known in the art without undue experimentation (*United States v. Telectronics,* Inc. 8 USPQD2d 1217 (Fed. Cir. 1988)). Whether undue experimentation is required is a conclusion reached by weighing several factors. These factors were outlined in *Ex parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Inter. 1986) and again in *In re Wands*, 8 USPQQ2d 1400 (Fed. Cir. 1988) and include the following:

Unpredictability of the art. The claimed methods embrace merely adding proteins (i.e. AAV helper functions of claim 3) to cultured cells or introducing proteins directly into cells (claim 10). The art concerning both of these method steps, particularly as applied to the instantly claimed methods, is unpredictable. The instant specification does not teach methods in which proteins are introduced directly into cells, but rather nucleic acids encoding the desired proteins are introduced. This is because of the difficulty of directly adding proteins to intact cells, which readily incorporate nucleic acids (e.g. in the form of precipitates, liposomes, viral genomes), but, with few exceptions, exclude proteins due to the barrier of the plasma membrane. Using methods and reagents similar to, or the same as, those instantly disclosed, Natsoulis et al (6,027,931, see below) introduced AAV or adenovirus nucleic acid sequences into cells by transfection or infection in order to produce rAAV or rAAV-producing cells. There is no disclosure of the direct introduction of such proteins into the cells by Natsoulis et al.

State of the art. The state of the art regarding the introduction of proteins directly into cells is poorly developed. The development of such methods and reagents would have to be done empirically.

Number of working examples. Applicants have provided no working examples of the introduction of proteins directly into cells.

Amount of guidance. Applicants provide no direction or guidance for the claimed methods of directly introducing proteins into cells. The specification requires the skilled artisan to practice trial and error experimentation with different methods, AAV and adenoviral proteins, and reagents to determine which (if any) will be introduced into the cells as claimed.

Scope of the invention. The claims are broad in nature and read on any step of merely "providing" helper functions" (i.e. claim 3) which can be adding the proteins to the same culture dish as the cells.

Nature of the invention. The invention involves the unpredictable art of directly introducing proteins into cells.

Level of skill in the art. While the level of skill in the art of introducing nucleic acids into cells is high, the level of skill in the art of directly introducing proteins into cells is low. The unpredictability of the art, lack of guidance, broad scope of the claims and poorly developed state of the art would require that undue and excessive experimentation would have to be conducted by the skilled artisan in order to practice the claimed invention.

Given the above analysis of the factors which the courts have determined are critical in determining whether a claimed invention is enabled, it must be considered that undue and

excessive experimentation would have to be conducted by the skilled artisan in order to practice the claimed invention.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-3, 10-13, 18, 21, 23, 24, 30, 32 and 33 are rejected under 35 U.S.C. 102(b) as being anticipated by Natsoulis et al (U.S. Patent 6,027,931, 2000). This rejection is maintained for reasons made of record in the previous Office Action and for reasons set forth below. New claims 32 and 33 are included in the rejection, necessitated by amendment of the claims. Claim 18 has been added because, absent evidence to the contrary and lacking a definition of "simian" in the specification, human cells and adenoviruses are considered simian. This is because of the taxonomic classification of humans under the Order "Simiformes", or simians.

Claims 1-2, 10-13, 18, 21, 23, 24, 30, 32 and 33 are rejected under 35 U.S.C. 102(b) as being anticipated by Xiao et al (J. Virol., 1998). This rejection is maintained for reasons made of record in the previous Office Action and for reasons set forth below. New claims 32 and 33 are included in the rejection, necessitated by amendment of the claims. Claim 18 has been added because, absent evidence to the contrary and lacking a definition of "simian" in the specification, human cells and adenoviruses are considered simian. This is because of the taxonomic classification of humans under the Order "Simiformes", or simians.

Response to Arguments

Applicant's arguments filed 1/3/2006 have been fully considered but they are not persuasive. Because the arguments relating to Natsoulis et al and Xiao et al are essentially the same, they addressed together. Applicants argue that Natsoulis et al does not teach all the limitations of the instant claims, specifically because the pRCM.globinpolyA vector, relied upon in the previous Office Action to demonstrate Rep 78/68 expression levels, does not express Rep 78/68 at about the level of wild-type/p5 expression. Rather, the pRCM.globinpolyA vector mediates Rep 78/68 expression levels that are less than those mediated by a wild-type/p5 promoter.

Applicants argue that Xiao et al does not teach all the limitations of the instant claims, specifically because the Rep 78/68 expression levels of Xiao et al are mediated by a mutated start codon, and therefore the Rep 78/68 expression levels of Xiao et al are less than those mediated by a wild-type/p5 promoter. Thus, the Rep 78/68 expression levels of Xiao et al are not "normal" expression.

Regarding these arguments, the claimed subject matter embraces a wide range of Rep 78/68 expression levels due to the use of the term "about the level of expression", and the lack of a definition of the term in the specification. Therefore, interpreted broadly, the scope of the claimed expression levels embraces situations where Rep 78/68 are expressed at levels less than those levels found in a wild-type situation. As detailed in the previous Office Action, both Natsoulis et al (Fig. 2) and Xiao et al (page 2226, first column, last paragraph) demonstrate expression of Rep 78/68 that are considered to be "about" the level when expressed from the p5 promoter, even though in both instances the Rep 78/68 expression may be less than the level

when expressed from the p5 promoter. It should also be noted that Rep 78/68 expression levels are not a limitation in claims 3, 10-13, 21, 23, 24, 30, 32 and 33.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 22, 26, 28, 29, 31, 35, 37, and 38 rejected under 35 U.S.C. 103(a) as being unpatentable over Natsoulis et al (6,027,931) as applied to claims 1-3, 10-13, 18, 21, 23, 24, 30, 32 and 33 above, and further in view of Hardy (U.S. Patent 6,429,001, 2002, effective filing date of 1/26/2000). This rejection is maintained for reasons made of record in the previous Office Action and for reasons set forth below. New claims 31, 35, 37, and 38 are included in the rejection, necessitated by amendment of the claims.

Claims 25 and 34 rejected under 35 U.S.C. 103(a) as being unpatentable over Natsoulis et al (6,027,931) as applied to claims 1-3, 10-13, 18, 21, 23, 24, 30, 32 and 33 above, and further in view of Murphy (U.S. Patent 6,635,476, 2003, effective filing date of 10/15/1999). This rejection is maintained for reasons made of record in the previous Office Action and for reasons set forth below. New claim 34 is included in the rejection, necessitated by amendment of the claims.

Claims 27-29 and 36-38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Natsoulis et al and Hardy as applied to claims 1-3, 10-13, 18, 21-24, 26, 28-33, 35, 37, and 38 above, and further in view of Potash et al (U.S. Patent 5,911,998, 1999). This rejection is maintained for reasons made of record in the previous Office Action and for reasons set forth below. New claims 36-38 are included in the rejection, necessitated by amendment of the claims.

Response to Arguments

Applicant's arguments filed 1/3/2006 have been fully considered but they are not persuasive. Applicants argue that since Natsoulis et al does not teach the claimed vectors that express levels of Rep 78/68 at wild-type levels in conjunction with Rep 52/40 overexpression, and that Natsoulis et al teach lower levels of Rep 78/68 expression correspond to higher titer of rAAV. Regarding these arguments, the issue of Rep 78/68 expression as taught by Natsoulis et al and the anticipation of claims 1-3, 10-13, 21, 23, 24, 30, 32 and 33 by the teachings of Natsoulis et al is addressed above. Furthermore, Rep 78/68 expression levels are not a necessary limitation in claims 22, 25-29, 31, and 34-38 because they depend (in part) from claims that do not recite the Rep 78/68 expression level limitation.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael D. Burkhart whose telephone number is (571) 272-2915. The examiner can normally be reached on M-F 8AM-5PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave Nguyen can be reached on (571) 272-0731. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Michael D. Burkhart
Examiner
Art Unit 1633

Scott D. Priebe

SCOTT D. PRIEBE, PH.D
PRIMARY EXAMINER